## REMARKS

Claims 1-20, 23, 26-28, 31, 36 are pending in the subject application with claims 26-28 and 37 withdrawn from consideration by the Examiner. Applicants have hereinabove canceled claims 2, 7, 8, 19, 20, 23, 26-28 and 37 without disclaimer or prejudice to applicants' right to pursue the subject matter of these claims in the future. Claim 1 has been amended hereinabove to incorporate the elements recited in previous claim 7. Claims 9 and 14 have been amended to make them depend from claim 1. In addition, applicants have added new claims 41 and 42. Support for new claims 41 and 42 can be found at page 12, lines 19-26. Applicants maintain that the amendments to the claims raise no issue of new matter. Accordingly, applicants respectfully request that this Amendment be entered.

### Restriction

In the February 12, 2009 Office Action the Examiner stated that Group I claims (claims 1-20, 23 and 36) as identified in the September 30, 2009 Restriction Requirement issued in connection with the above-identified application will be joined with the Group III claim (claim 31) for examination.

### Claims Rejected Under 35 U.S.C. §103(a)

Claims 1-3, 7-10, 14, 15, 19, 20 and 23

The Examiner rejected claims 1-3, 7-10, 14, 15, 19, 20 and 23 as allegedly obvious over Reed et al. (PNAS 92:9455-9459, (1995)) in view of Hoffman et al. (U.S. Patent No. 5,545,727, issued 1996) "as evidenced by [a] sequence search result." The Examiner stated, *inter alia*, that Reed et al. teach that the functional domain of p53 forms dimmers or a stable tetramer, and that the C-terminal of p53 contains amino acids 318-393 of human p53. The

Examiner also stated that "Reed et al., also suggest that the dimer or tetramer is formed as a mirror structure (figure 4), i.e. dimer comprised [of] the tetramer would be formed by linking the sequence of SEQ ID NO:1 to its palindrome sequence of SEQ ID NO:2 as 5'-3'-linking—5'-3', that is equal or the same to a peptide formed by linking two SEQ ID NO:1 as 5'-3'—linking--3'5'." (emphasis in original).

The Examiner acknowledged that Reed et al. do not teach that "the peptides of dimers or tetramer are covalently linked by a single glycine linker." However, the Examiner asserted that Hoffman et al. teach a method of making a fusion protein or multimers by crosslinking or covalently linking by a single glycine linker and teach an advantage of using glycine. The Examiner cited the Search Sequence to show that SEQ ID NO:1 is a 41 amino acid peptide of a "C-terminal fragment of p53 protein" at residue positions 353-393.

*Applicants' Response*

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution and without conceding the correctness of the Examiner's position, applicants have hereinabove amended claim 1, from which the remaining rejected claims depend, to recite a specific polypeptide sequence.

Applicants note that Reed et al. discloses a tetramer, not a single polypeptide with continuous amino acids as claimed. As shown in Fig. 4 of Reed et al., the tetramer of Reed et al. is four non-covalently associated peptide subunits orientated in a N:N or a C:C fashion, i.e. not permitting peptide bond formation between the termini. In contrast, claim 1 recites a single N-C polypeptide which comprises amino acids corresponding to amino acids 353 to 393 of p53 covalently linked to a repeat

corresponding to amino acids 393 to 353 of p53, i.e. a repeat in the reverse sequence order with respect to the one preceding it, but, because it is a single polypeptide, still maintaining N-C orientation. There is no teaching or suggestion in the prior art to link amino acids corresponding to amino acids 353 to 393 of p53 in a N-C orientation to a repeat corresponding to amino acids 393 to 353 of p53. More importantly, the prior art offers no information allowing one of ordinary skill to predict the properties of such a polypeptide.

In addition, the p53 tetramer is in contrast to the claimed polypeptide. In specific regard to the differences between a p53 tetramer and a single polypeptide, applicants enclose herewith as **Exhibit 1** a copy of LaFevre-Bernt et al. which discusses the nature of the non-covalent p53 tetramer. Page 1425 of Example 7 of Exhibit 1 states that "It is well known that the p53 protein tetramizes through a noncovalent dimer model". In addition, Hoffman et al., cited by the Examiner for teaching glycine linkers, would not solve this deficiency in the teaching of Reed et al. if combined therewith because the glycine linker would not link an N-terminal to an N-terminal, or a C-terminal to a C-terminal, of the p53 tetramer shown in Reed et al. Thus, the teachings of the combination of cited art therefore do not render the invention as claimed obvious.

Additionally, applicants note that the combination of Reed et al. and Hoffman et al. does not teach or suggest a polypeptide that corresponds to (a) deleting a stretch of amino acids from the **318**-393 amino acid portion of human p53 disclosed in Reed et al. (page 9456, right hand column, last line), (b) joining four of such truncated stretches together as a single polypeptide, while (c) reversing the order of a repeat. Applicants note that there is no suggestion or teaching in the combination of cited art that anything less than Reed's reported **318**-393 amino acid residue

portion of human p53 would be effective to recognize damaged DNA, which is the asserted basis of the properties of p53 according to Reed et al. (see Discussion on page 9458).

Applicants additionally note that Reed et al. teach that the p53 tetramer (four different molecules non-covalently associated together) binds the DNA (see Fig. 4, see page 9459) and indicates that the cited tetramerization region (see Fig. 4 and pages 9458-9459) which is "needed for DNA binding to the C-terminal region" (see page 9459, left hand column) is amino acids **318-355** (see Fig. 4). In contrast, the claimed polypeptide corresponds to repeats of only amino acids **353-393** of p53 (except that the second repeat is in the reverse order relative to the preceding one). One of ordinary skill in the art, in light of the cited disclosure in Reed et al., could not predict that one could take the tetramer of Reed et al., remove different specific portions of the amino acids sequences of the subunits apparently required for function, and then bond the various truncated portions together to assemble a single polypeptide and still reasonably expect the resulting molecule to have the functionality described in Reed et al. The combination of Hoffman et al. with Reed et al. does not cure these deficiencies.

Finally, applicants note that the generic disclosure in Hoffman et al. of glycine linkers shows (in col. 34 cited by the Examiner) a polypeptide including at least one triple glycine linker, and in Example 26, cited by the Examiner, shows a glycine *or* proline linkage. The February 12, 2009 Office Action provides no reasoning as to why one skilled in the art would specifically chose single glycines over the triple glycines, or glycine in preference to proline, to be the only linkers for attaching the peptides to somehow arrive at the claimed polypeptide, and Reed et al. in combination with Hoffman et al. does not cure this deficiency.

The specific polypeptide claimed is not taught or suggested by, and is therefore not obvious over, the cited combination of prior art. Accordingly, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Claims 1, 4-9, 11-14, 16-18, 31 and 36

The Examiner rejected claims 1, 4-9, 11-14, 16-18, 31 and 36 as allegedly obvious over Reed et al. (PNAS 92:9455-9459, (1995)) in view of Hoffman et al. (U.S. Patent No. 5,545,727, issued 1996) "as evidenced by [a] sequence search result as applied to claims 1, 7-9, 14 and further in view of Pincus, M. (WO2003/105880, filed March 2003, claiming priority to March 2002, published December 2003).

Applicants note that although the Examiner rejected claims 1, 4-9, 11-14, 16-18, 31 and 36 over this combination of cited art, the Examiner only described why claim 31 was rejected (see pages 6-8 of the Office Action). However, applicants have hereinbelow explained why claims 1, 4-9, 11-14, 16-18, 31 and 36 are patentable over the cited combination of art, and Pincus combined with Reed et al. and Hoffman et al. do not overcome the problems.

The Examiner stated that the teachings of Reed et al. and Hoffman et al. are as explained previously. The Examiner further stated that Pincus et al. teach a membrane penetrating leader sequence identical to SEQ ID NO:8 of the present application and its fusion to the C-terminus of a fusion polypeptide comprising a p53 fragment and also teaches a pharmaceutical composition comprising the fusion peptide for killing cancer cells or treating a cancer patient. The Examiner asserted it would have been obvious to one of ordinary skill in the art to fuse the carrier peptide to the "dimers or tetramer (SEQ ID NO:3-7)" with "expected" results, although did not explain what the expected results were.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution and without conceding the correctness of the Examiner's position, applicants have hereinabove amended claim 1, from which the remaining rejected claims depend, to recite a specific polypeptide sequence.

Applicants note that Reed et al. discloses a tetramer, not a single polypeptide with continuous amino acids as claimed. As shown in Fig. 4 of Reed et al., the tetramer of Reed et al. is four non-covalently associated peptide subunits orientated in a N:N or a C:C fashion, i.e. not permitting peptide bond formation between the termini. In contrast, claim 1 recites a single N-C polypeptide which comprises amino acids corresponding to amino acids 353 to 393 of p53 covalently linked to a repeat corresponding to amino acids 393 to 353 of p53, i.e. a repeat in the reverse sequence order with respect to the one preceding it, but, because it is a single polypeptide, still maintaining N-C orientation. There is no teaching or suggestion in the prior art to link amino acids corresponding to amino acids 353 to 393 of p53 in a N-C orientation to a repeat corresponding to amino acids 393 to 353 of p53. Moreover, the attachment of the membrane-penetrating sequence disclosed by Pincus et al. to the sequence disclosed in Reed et al. & Hoffman et al. would not result in or render obvious applicant's different claimed sequence. More importantly, the prior art offers no information allowing one of ordinary skill to predict the properties of such a polypeptide.

In addition, the p53 tetramer is in contrast to the claimed polypeptide. In specific regard to the differences between a p53 tetramer and a single polypeptide, applicants enclose herewith as **Exhibit 1** a copy of LaFevre-Bernt et al. which discusses the nature of the non-covalent p53 tetramer. Page 1425 of Example 7

of Exhibit 1 states that "It is well known that the p53 protein tetramizes through a noncovalent dimer model". In addition, Hoffman et al., cited by the Examiner for teaching glycine linkers, would not solve this deficiency in the teaching of Reed et al. because the glycine linker would not link an N-terminal to an N-terminal, or a C-terminal to a C-terminal, of the p53 tetramer shown in Reed et al. Thus the teachings of the combination of cited art therefore do not render the invention as claimed obvious. Pincus et al. in combination with Reed et al. and Hoffman et al. does not cure the failure of the combination to teach, suggest or render obvious the claimed sequence.

Additionally, applicants note that the combination of Reed et al. and Hoffman et al. does not teach or suggest a polypeptide that corresponds to (a) deleting a stretch of amino acids from the **318**-393 amino acid portion of human p53 disclosed in Reed et al. (page 9456, right hand column, last line), (b) joining four of such truncated stretches together as a single polypeptide, while (c) reversing the order of a repeat. Applicants note that there is no suggestion or teaching in the combination of cited art that anything less than Reed's reported **318**-393 amino acid residue portion of human p53 would be effective to recognize damaged DNA, which is the asserted basis of the properties of p53 according to Reed et al. (see Discussion on page 9458). Pincus et al. in combination with Reed et al. and Hoffman et al. does not cure the failure of the combination to teach, suggest or render obvious the claimed sequence.

Applicants additionally note that Reed et al. teach that the p53 tetramer (four different molecules non-covalently associated together) binds the DNA (see Fig. 4, see page 9459) and indicates that the cited tetramerization region (see Fig. 4 and pages 9458-9459) which is "needed for DNA binding to the C-terminal region" (see page 9459, left hand column) is amino acids **318-355** (see

Fig. 4). In contrast, the claimed polypeptide corresponds to repeats of only amino acids **353-393** of p53 (except that the second repeat is in the reverse order relative to the preceding one). One of ordinary skill in the art, in light of the cited disclosure in Reed et al., could not predict that one could take the tetramer of Reed et al., remove different specific portions of the amino acids sequences of the subunits apparently required for function, and then bond the various truncated portions together to assemble a single polypeptide and still reasonably expect the resulting molecule to have the functionality described in Reed et al. The combination of Pincus et al. with Hoffman et al. and Reed et al. does not cure these deficiencies.

Finally, applicants note that the generic disclosure in Hoffman et al. of glycine linkers shows (in col. 34 cited by the Examiner) a polypeptide including at least one triple glycine linker, and in Example 26, cited by the Examiner, shows a glycine *or* proline linkage. The February 12, 2009 Office Action provides no reasoning as to why one skilled in the art would specifically chose single glycines over the triple glycines, or glycine in preference to proline, to be the only linkers for attaching the peptides to somehow arrive at the claimed polypeptide, and Reed et al. in combination with Hoffman et al. and Pincus et al. does not cure the failure of the combination to teach, suggest or render obvious the claimed sequence.

The specific polypeptide claimed is not taught or suggested by, and is therefore not obvious over, the cited combination of prior art. Accordingly, applicants respectfully request reconsideration and withdrawal of this ground of rejection.

Claims 4-9, 11-14, 16-18, and 36, which depend from claim 1, are not obvious in at least because the subject matter of claim 1 is not obvious.

Claim 31, which requires the limitations of claim 1, and which is directed to a method of treating a subject suffering from cancer, is not obvious in at least because the subject matter of claim 1 is not obvious. Additionally, the subject matter of claim 31 is not obvious also because Pincus et al. does not disclose or suggest that repeating p53 fragment or palindromic p53 fragment peptides, or polypeptides corresponding thereto, attached to a membrane-penetrating sequence could be used to treat cancer. This is speculation by the Examiner and is not supported by the cited art; the Examiner's speculated result is not predictable from the prior art. Moreover, the in vivo results described in the specification (e.g. see page 29, line 24 to page 30, line 5 and Fig. 10) showing statistically significant increases in survival times of cancerous animals is neither suggested nor predicted by the combination of cited art. Applicants note that Pincus et al. use residues 17-26 of p53 (see Table 3, page 22 of Pincus et al.), which Pincus notes binds to a different target (i.e. MDM-2 - see page 2 of Pincus et al.) than the p53 DNA-binding domain, and which is different from the p53 homotetramer domain (see Page 1 of Pincus et al.). As such it is not predictable from the cited combination of prior art that a <u>different</u> portion of the p53, much less a repeating p53 fragment or palindromic p53 fragment peptide with or without a membrane-penetrating sequence fused thereto, could be used to successfully treat a cancer.

Accordingly, applicants respectfully request reconsideration and withdrawal of this ground of rejection.